REMARKS/ARGUMENTS

In the Office Action mailed April 23, 2010, claims 19-21 and 37-39 have been allowed and claims 23-36 and 40-43 stand rejected. Applicants thank the Examiner for indicating the allowability of claims 19-21 and 37-39 and respectfully submit that claims 23-36 and 40-43 are allowable in light of the following. Without conceding the propriety of the reject of claims 23-36 and 40-43, claims 33 and 40-43 have been amended. The amendments to claim 33 are supported, at least at, page 8, lines 4 to 11; page 11, lines 22 to 26; and page 14, lines 4 to 19. The amendments to claims 40-43 are of a minor typographical nature. Accordingly, no new matter has been added and no estoppels intended thereby.

Applicants have thoroughly reviewed the outstanding Office Action including the Examiner's remarks and the references cited therein. The following remarks are believed to be fully responsive to the Office Action.

CLAIM REJECTIONS – 35 U.S.C. §112

Claims 22-36 and 40 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, claims 40-43 are alleged to be unclear with respect to what is being claimed concerning the "sequences of ≥ 80% homology to said dominant sequence," because only the dominant sequence is tested for confirming that it bind specifically to said antigen of *C. difficile*. Applicants respectfully traverse this rejection.

Initially, it is to be noted that that the B cells that are obtained from a patient in step (i) of claims 40-43 are representative of the entire T-cell repertoire of the patient. Consequently, some, perhaps many, of the B cells will produce antibodies which are not specific to the antigen

produced by *C. difficile*. The "set of sequences" which is defined in step (ii) reflects the maturation process and the clonal expansion process which naturally take place in the immune system of an individual when presented with an antigen such as an antigen of *C. difficile*. Multiple different B cells are produced but those which generate antibodies which target the antigen are clonally expanded and tend to have similar sequences of their CDR3 regions since it is the CDR3 region which is primarily responsible for antigen binding specificity of antibodies. Thus by identifying a set of sequences which are similar in sequence (i.e. dominant sequence and sequences having at least 80% homology to the dominant sequence) it is possible to identify sequences which are responsible for the binding specificity of antibodies to the antigen in question.

It is further alleged that "only the dominant sequence is tested for confirming that it bind [sic] specifically to said antigen of *C. difficile*", (see section 7 of the office action). However, this does not affect the working of the invention for two reasons. Firstly, antibodies with CDR3 regions having sequences of at least 80% homology can reasonably be expected to target the same antigen. Secondly, the purpose of the method as defined in claim 40 is to identify the dominant sequence. By referring also to sequences having at least 80% homology to the dominant sequence, a skilled person is able to identify the dominant sequence. This is because the maturation process that takes place during an immune response improves antigen binding by altering the sequence of CDRs. Thus the CDR3 sequence of an antibody which is specific for a target antigen is often characterized by the presence of other CDR3 sequences having a high level of homology thereto. To take a specific example, if the dominant sequence occurs in a frequency of 0.7% and the frequency of the sequences having at least 80% homology to the dominant sequence occur in a frequency of 0.4% then the frequency of the set of sequences is

1.1% and therefore falls within the scope of the claim (being greater than "at least 1%"). However, if the sequences having at least 80% homology to the dominant sequence were not taken into account then the set would not fall within the scope of step (ii) because the total frequency would be 0.7% which is less than "at least 1%". This is also explained in page 7, line 20 to page 8, line 2 of the published PCT application.

It is also to be understood that, "detecting a set of sequences that occur in total at a frequency of at least one percent, wherein the set of sequences include a dominant sequence and sequences of at least 80% homology to the dominant sequence" as recited in step (ii) is not a mere arbitrary feature but is reflected in the operation of the present invention. For example, referring to Table 2 on page 38 of the published PCT application, library D01 (obtained from patient D01) identified several sequences (SEQ. ID NOS. 27, 35, 36 and 37) which had 100% similarity to each other and a further sequence (SEQ. ID NO. 38) which had 93.75% similarity to the other sequences. One hundred and eighty-four clones comprising SEQ. ID NO. 27 were identified; three clones of SEQ. ID NO. 36 and one clone each of SEQ. ID NOS. 35, 37 and 38. Similarly, referring to Table 3, it can be seen that SEQ. ID NO. 28 was identified in 43 clones of library D01 whereas one clone was identified of SEQ. ID NO. 39 (which has 100% similarity to SEQ. ID NO. 28) and one clone was identified of SEQ. ID NO. 40 which has 88.88% similarity to SEQ. ID NO. 28. Thus it can be seen that the clonal proliferation and focussing of B cells during an infection by *C. difficile* gives rise to a distinct set of CDR3 sequences in the antibodies of the B cell repertoire of the patient which have a high degree of homology to each other but which comprise one particular dominant sequence (e.g. SEQ. ID NOS. 27 and 28 in the examples shown in Tables 2 and 3). In this regard, the antibodies comprising CDR3 sequences which have less than 100% homology to the dominant sequence are likely to have a lower

binding affinity for the antigen than the dominant sequence and this is why B cells producing the antibody are present at a lower frequency in the B cell repertoire of the patient.

Accordingly, the reference to the sequences having at least 80% homology to the dominant sequence does not give rise to a lack of clarity because the homologous sequences do play a role in the identification of the set of sequences even though it is the dominant sequence of the set that is most likely to have the highest affinity for the antigen and is therefore tested in step (iii).

Claim 33 stands rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP §2172.01. The omitted steps are: methods of identifying sequences which are effective to clear *C. difficile.* Claim 33 has been amended to remove the element, "are effective to clear the infection". Furthermore, claim 33 has been amended to clarify how the comparison of sequences from the first and second patients is carried out. More specifically, sets of sequences are prepared from a first patient who has recovered from infection by *C. difficile* and a second patient who has not recovered from infection by *C. difficile.* A set of sequences is identified that is present in the first patient but not in the second patient. This preferred sequence is thus *prima facie* a sequence that was able to clear the infection in the first patient and its absence in the second patient is the reason why the second patient is still infected. Thus this preferred sequence is tested for binding to an antigen produced by *C. difficile.* Support for these amendments are found, at least at, page 8, lines 4 to 11; page 11, lines 22 to 26; and page 14, lines 4 to 19. Accordingly, Applicants believe that the rejection of claim 33 has been overcome and earnestly solicit allowance thereof.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request that all the objections and rejections to the claims be removed and that the claims pass to allowance. If, for any reason, the Examiner disagrees, please call the undersigned at 202-861-1629 in an effort to resolve any matter still outstanding before issuing another action. The undersigned is confident that any issue which might remain can readily be worked out by telephone.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiencies or credit any overpayments to Deposit Account No. 50-2036 with reference to our Docket No. 87278.2760.

Respectfully submitted,
BAKER & HOSTETLER LLP

Michael D. Graham
Reg. No. 51,750

Date: October 22, 2010
Washington Square, Suite 1100
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036-5304
Telephone: 202-861-1500
Facsimile: 202-861-1783

103432051.1